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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/277,064	03/26/1999	LINDA A. SHERMAN	TSRI.433.1-D	3058

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THE SCRIPPS RESEARCH INSTITUTE
10550 NORTH TORREY PINES ROAD
MAIL DROP TPC 8
LA JOLLA, CA 92037

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/277,064	SHERMAN, LINDA A.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant s submission filed on 04/26/04 has been entered.

Accordingly, claim1 is being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC112, first paragraph of claim 1 pertaining to lack of enablement for a method for in vivo activating of specific cytotoxic T lymphocytes remains for reasons already of record in paper of 06/17/03.

Applicant asserts that by typographic error, the Office action refers to SEQ ID NO:10, whereas the correct sequence of the instant claim is SEQ ID NO:12.

The Examiner apologizes for this inadvertent typographic error. The correct sequence in the instant claim is SEQ ID NO:12.

Applicant argues that because pending claim I does not recite the limitation of "targeting or killing of malignant cells that express Her-2/neu in an animal having a

tumor burden that express Her-2/neu", the present rejection is irrelevant and should be withdrawn because Applicant does not have the responsibility to enable that which is not claimed.

Applicant argues that Example 5 demonstrates that immunizing an animal with the polypeptide of SEQ ID NO:12 specifically activates cytotoxic T lymphocytes (CTLS) in vivo (see e.g., pages 101-111 and Figures 13A and 13B of the specification). Applicant concludes that thus, there can be no determination of undue experimentation because no experimentation is required to practice the claimed invention, as amended above.

Applicant's arguments set forth in paper of 02/26/04 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that SEQ ID NO:12 is a fragment of the Her-2/neu protein.

The amended **claim 1 still reads on a method of in vivo activating cytotoxic T lymphocytes in an animal, which is a cancer patient, for the purpose of cancer treatment, as contemplated in the specification.**

Although Example 5 demonstrates that injection of SEQ ID NO:12 into transgenic mice A2.1/Kb xCD8, or A2.1 produces CTLS that could lyse some tumor cell lines that express both A2.1 and Her-z/neu, the CTLS are xenogeneic (specification, p.101), and the mice do not have cancer. As discussed in previous Office action, in a situation where Her-2/neu is a self-protein, such as in mice that have tumors that express HER/Neu, self-tolerance could eliminate T cells that are capable of recognizing Her-2/neu protein with high avidity. Thus unless tested, it is unpredictable that mice

having tumors that express HER/Neu would produce CTLs specific for SEQ ID NO:12 with high affinity. Since the surviving CTLs would have low affinity to the claimed SEQ ID NO:12, one would not be able to predict that said CTLs with low affinity for SEQ ID NO:12 would be able to eliminate tumor cells *in vivo* (Sherman et al, of record, and the specification on page 101, lines 10-25). This inability of CTLs with low affinity to eliminate tumor cells *in vivo* would be even further exacerbated by tumors cells that either are not efficient in antigen presentation, similar to the tumor cell lines disclosed in the specification (p.106, lines 19-36), or tumor cells that do not express the specific tumor antigen due to an autochothonuous immune response (see discussion below, Cheever et al, of record, column 9, first paragraph). Further, as admitted by Applicant, after some period of time in the presence of tumor cells, T cells could lose their functional activity (specification, p.101).

In addition, one could not extrapolate the *in vitro* tumor cell line killing by CTLs of the claimed invention with *in vivo* tumor cell killing due to the following reasons:

1) Characteristics of tumor cell lines *in vitro* are different as compared to primary tumor cells (Freshney et al, Dermer et al, of record). Further, although *in vitro* a tumor cell line can express the peptide of SEQ ID NO:12 from Her-2/Neu protein, the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, could be subsequently lost, because an effective autochothonuous immune response can convert a Her-2/Neu positive tumor to Her-2/Neu negative (Cheever et al, of record, column 9, first paragraph). Thus it is unpredictable that mice with Her-2/Neu tumor burden actually express or have adequate amount of Her-2/Neu protein on the tumor

cell surface. Applicant however has not shown that in vivo primary tumor cells actually present or have adequate amount of the peptide of SEQ ID NO:12 on the cell surface,

2) I*n vitro* and *in vivo* environment is different, and

3) conditions for targeting tumor cells are different, wherein in *in vitro* the tumor cells are continuously exposed to the CTLs and in the presence of cytokines to increase the sensitivity of lysis by CTLs (Freshney et al, Dermer et al, of record). Further, as taught by Boon et al (of record), even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Thus it is unpredictable that cytotoxic T lymphocytes that are not xenogeneic would be activated in an animal with a tumor burden that expresses Her-2/neu; wherein said cytotoxic T lymphocytes could target or kill primary malignant cells that express a Her-2/Neu protein *in vivo* for cancer therapy as contemplated in the specification.

Moreover, one would not know how to use the CTLs produced in the transgenic, xenogeneic, cancer-free mice disclosed in the specification, because one cannot predict that said CTLs could kill primary target cancer cells, and because cancer therapy is unpredictable, for the reasons set forth above.

In summary, in view of the above discussion, and further in view of the unpredictability of tumor vaccination and anticancer drug discovery, as overwhelmingly evidenced by Ezzell et al, Spitler et al, Boon et al, Gura et al, Jain et al, Curti et al, and Hartwell et al (of record), it would have been undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Grey et al, of record.

Claim 1 is drawn to a method for specifically activating cytotoxic T lymphocytes in vivo, comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:12.

Grey et al teach injection into transgenic mice putative CTL epitopes for inducing specific CTLs, and testing for lysis of peptide-coated target cell line Jurkat that expresses the A2 KB molecules (p. 76 and table 24). Grey et al also teach identification of immunogenic peptides, wherein one of the identified peptide is VMAGVGSPYV (p. 108, sixth sequence) which is from c-ERB2 (or Her-2/Neu), and has A2 binding affinity of 0.018 and which is exactly the same as the claimed SEQ ID NO:12 (Example 12 on page 79 and page 108, sixth sequence). Grey et al further teach that based the results on table 24, peptides that have a binding of at least 0.01 are capable of inducing CTLs (page 76, last paragraph).

Thus the method taught by Grey et al seems to be the same as the claimed method.

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

June 30, 2004